REMARKS

Claims 1-22 were pending in this case. With this reply, claims 1-22 have been cancelled and claims 23-37 have been added. Thus, claims 23-37 are now pending and under examination. All of claims 23-37 are directed to the subject matter of restriction group I (i.e., the tricyclic ring structure). The Office objects to the specification. Claims 1-11 stand rejected under 35 U.S.C. § 101 for lack of utility. Claims 1-11 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. Claims 1-11, 14-16, 18, and 19 stand rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. Claims 1-11 stand rejected under 35 U.S.C. § 102(b) for lack of novelty. Claims 18-20 and 22 stand rejected under 35 U.S.C. § 103(a) for obviousness. Finally, claims 1-11, 18-20, and 22 stand rejected for nonstatutory obviousness-type double patenting. The objection and each of these rejections are addressed below.

Objections to the Specification

The Office objects to the specification for failure to include an abstract and for the section heading entitled "Legend to figures." Applicants have addressed each of these objections by amendment of the specification.

With this reply, the specification has been amended to replace at page 30, line 25, the heading "Legend to figures" with "Brief description of drawings," as proposed by the Examiner.

The specification has also been amended to include an abstract. Applicants note that an abstract in English was submitted with the PCT application at the time of the national stage filing, but was not included with the translated specification. This application has published as U.S. Patent Publication No. 20050176747 with this same PCT Abstract. With this reply, Applicants have amended the specification to incorporate an abstract identical to the published abstract.

In view of the amendments to the specification, Applicants request that these

objections to the specification be withdrawn.

Rejections under 35 U.S.C. § 101

Claims 1-11 stand rejected under 35 U.S.C. § 101 for lack of utility. The basis for this rejection is the claimed recitation of a use without setting forth any steps involved in the process. Applicants have addressed this rejection by amendment of the claims.

With this reply, claims 1-22 have been cancelled and claims 23-37 have been added. Claims 23-33 are directed to methods of treating and include the step of administering a compound of formula (Ia) to a subject. Claims 34-37 are directed to compositions. As amended, the method claims now recite a specific step in the process of treating a subject.

In view of the amendments to the claims and the remarks above, Applicants request that the rejection for lack of utility be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-11 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. This is a two-part rejection. First, the claims are rejected for lack of enablement with respect to the use of 'derivatives' (e.g., hydrates, solvates, and prodrugs). Second, the claims are rejected for lack of enablement with respect to treating any and all known vascular disorders or respiratory disorders. Applicants have addressed these rejections by amendment of the claims and with the following remarks.

As a first basis for rejection, the Office rejects the method claims for being directed to the use of unenabled 'derivatives' (e.g., hydrates, solvates, and prodrugs). Applicants respectfully disagree.

The original method claims were directed to the use of compounds having a particular formula, not their derivatives or specific forms of the compound. For the sake of clarity in the newly added method claims, claims 23-33, the term 'compound' is

utilized, rather than the term 'derivative.' Applicants note that the previously pending method claims were never directed to the use of specific forms, such as hydrates or solvates, or to the use of prodrugs. Rather, the claims were directed to the use of compounds of a particular formula. As such, the use of the term 'compound' in favor of the term 'derivative' in the presently amended claims does not, by itself, surrender any claim scope over the previously pending claims. For example, new claims 23-33 are directed to methods of treating by administering a compound of a particular formula. The claims are silent with respect to the use of specific forms of the compounds (such as hydrates and solvates), the claims do encompass these possible future improvements of the claimed method. Such subject matter has not been surrendered with the present amendment to the claims.

As a second basis for rejection, the Office rejects the method claims for lack of enablement with respect to treating any and all known vascular disorders or respiratory disorders. As a basis for this rejection the Office Action at pages 5 and 6 states:

> ...the specification teaches that the instant compounds are activators of CFTR channel. There is no teaching or guidance present in the specification or prior art that hypoactivity of CFTR channel is implicated in the etiology of every known vascular disorder or respiratory disorder. There is no teaching in the prior art that structurally closely related compounds having CFTR channel activating activity are well known to have therapeutic utility in treating every known vascular disorder or respiratory disorder including arterial hypertension and asthma. There are no working examples present showing efficacy of instant compounds in known animal models of every known vascular disorder or respiratory disorder including arterial hypertension and asthma.

Applicants respectfully disagree.

Applicants have discovered that benzo[c]quinolizinium compounds are capable of relaxing smooth muscle cells (see, for example, the specification at page 2, lines 3-15). It is this relationship between benzo[c]quinolizinium compounds and relaxation of smooth muscle cells that is the basis for concluding that benzo[c]quinolizinium compounds can be useful for the treatment of disorders associated with the constriction of smooth muscle cells, such as arterial hypertension and asthma.

Applicants note that new claims 23-33 are directed to methods of treating a pathology associated with the constriction of smooth muscle cells, not every known vascular disorder or respiratory disorder.

The common underlying relationship between smooth muscle contractility and disorders such as asthma and hypertension is well established (see Medici et al., *Chest* 104:1138 (1993), included herewith, which teaches, in the abstract on page 1138, that both hypertension and asthma are spastic disorders of smooth muscles and that both conditions are worsened by high salt diets). The relationship between smooth muscle contractility and asthma has been known since 1840 (see the historical note by Lotvall (*Eur. Respir. J.*, 7:592 (1994)), included herewith). Lotvall reports that medicaments used for the treatment of asthma in the nineteenth century, such as stramonium, belladonna, and opium were all shown to inhibit air tube contractility (see Lotvall at page 594). Although these medicaments are now known to operate via different underlying mechanisms, they all share this common effect on smooth muscle contractility. Accordingly, one of skill in the art would expect, based solely upon the in vitro data provided by the Applicant, that a compound shown to relax smooth muscle cells is a potentially useful therapeutic for the treatment of disorders associated with the constriction of smooth muscle cells, such as arterial hypertension and asthma.

Applicants' in vitro data showing that benzo[c]quinolizinium compounds are capable of relaxing smooth muscle cells, in combination with the state of the art at the time of filing, is sufficient to enable one of skill in the art to use the claimed compounds for the treatment of disorders associated with the constriction of smooth muscle cells, such as arterial hypertension and asthma.

In view of the amendments to the claims and the remarks above, Applicants request that the rejections for lack of enablement be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-11, 14-16, 18, and 19 stand rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. This is a three-part rejection: (i) claims 1-11, 14-16, 18, and 19 are rejected for reciting both broad and narrow limitations for a particular variable; (ii) claims 2-4, 7, 8, and 15 are rejected for insufficient antecedent basis in the term -$NHCOCH_3$; and (iii) claims 1-11 are rejected for failing to set forth any steps involved in the claimed methods. Applicants have addressed each of these rejections by amendment of the claims.

With this reply, claims 1-22 have been cancelled and claims 23-37 have been added. These newly added claims have been corrected for each of the deficiencies identified by the examiner in the previously pending claims.

In view of the amendments to the claims, Applicants request that the rejections for indefiniteness be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 1-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Becq (WO 98/05642; hereinafter "Becq 1998"). As a basis for this rejection the Office Action at page 8 states:

> Becq discloses CFTR channel activator compounds, pharmaceutical compositions containing these compounds and their use for treating cystic fibrosis. The pharmaceutical compositions containing compounds disclosed on pages 14-21 by Becq anticipate the instant claims when R5 represents variables other than an ester in the instant compounds of formula (I).

Applicants have addressed this rejection by amendment of the claims.

With this reply, claims 1-22 have been cancelled and claims 23-37 have been added. Claims 23-33 are directed to the use of benzo[c]quinolizinium compounds for treating disorders associated with the constriction of smooth muscle cells, such as arterial hypertension and asthma. In contrast Becq 1998 teaches the use of benzo[c]quinolizinium compounds for treating disorders associated with dysfunctional

ionic flux, such as cystic fibrosis.

The instant invention is the result of Applicants' discovery that benzo[c]quinolizinium compounds are capable of relaxing smooth muscle cells and, therefore, can be useful for the treatment of conditions associated with vasoconstriction, such as hypertension (a vascular disorder associated with vasoconstriction of the blood vessels) and asthma (a respiratory disorder associated with bronchoconstriction). Becq 1998 fails to teach or suggest that benzo[c]quinolizinium compounds are capable of relaxing smooth muscle cells.

Claims 34-37 are directed to specific compounds, and pharmaceutical compositions containing the specific compounds, which the Examiner has already found novel over Becq 1998.

In view of the amendments to the claims and the remarks above, Applicants request that the rejections for lack of novelty be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 18-20 and 22 stand rejected under 35 U.S.C. § 103(a) as obvious over Becq (U.S. Patent 6,630,482; hereinafter "Becq 2003"). As a basis for this rejection the Office Action at page 9 states:

> Becq discloses CFTR channel activator compounds, pharmaceutical compositions containing these compounds and their use for treating cystic fibrosis. The compounds of formula (III) disclosed in column 10, lines 1-17 as well as compounds 12, 18-21 and 25-27 (see columns 11-13) disclosed by Becq meet all the limitations of instant claims except that variable Y represents SH group in the instant claims instead of an OH group. However, both oxygen and sulphur atoms belong to the same class of chalcogens. Therefore, it would have been obvious to one skilled in the art to prepare the instant compounds substituted with SH group at 6th position instead of an OH group without affecting their utility of activating CFTR channels with reasonable expectation of success.

Applicants have addressed this rejection by amendment of the claims.

With this reply, claims 1-22 have been cancelled and claims 23-37 have been added.

Claims 23-33 are directed to methods for treating and are not relevant to this rejection for obviousness.

Claims 34 and 36 are directed to specific compounds, and pharmaceutical compositions containing the specific compounds, and correspond to the subject matter of previously pending claim 17, which the Examiner has found allowable.

Claims 35 and 37 are directed to two specific benzo[c]quinolizinium compounds, MPB 102 and MPB103, in which Y of formula (Ia) is –SH. The two compounds include specific structural features, such as a chlorine atom at position 10, a thiol at position 6, and an n-butyl group at position 5. The particular combinations of structural features found in the two compounds claimed are neither taught nor suggested by Becq 2003.

In view of the amendments to the claims and the remarks above, Applicants request that the rejections for obviousness be withdrawn.

Obviousness-type Double Patenting

Claims 1-11, 18-20, and 22 stand rejected for nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of Becq 2003. As a basis for this rejection the Office Action at page 9 states:

> Claims 1-11, 18-20 and 22 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,630,482. Although the conflicting claims are not identical, they are not patentably distinct from each other because the pharmaceutical composition for activating CFTR channels containing compounds of claim 1 of the cited patent anticipate the instant claims 1-11 when instant variable R^5 is either H or other than an ester and furthermore, it would have been obvious to one skilled in the art to prepare the instant compounds of claims 18-20 and 22 substituted with SH group at 6^{th} position instead of an OH group without affecting their utility of activating CFTR channels with reasonable expectation of success since both oxygen and sulphur atoms are chalcogens.

Applicants have addressed this rejection by amendment of the claims.

With this reply, claims 1-22 have been cancelled and claims 23-37 have been added.

Claims 23-33 are directed to the use of benzo[c]quinolizinium compounds for

treating disorders associated with the constriction of smooth muscle cells, such as arterial hypertension and asthma. In contrast, claim 1 of Becq 2003 is directed to a list of specific compounds. Neither the specification nor the subject matter in claim 1 of Becq 2003 teaches or suggests that benzo[c]quinolizinium compounds are capable of relaxing smooth muscle cells.

Claims 34 and 36 are directed to specific compounds, and pharmaceutical compositions containing the specific compounds, and correspond to the subject matter of previously pending claim 17, which the Examiner has found allowable.

Claims 35 and 37 are directed to two specific benzo[c]quinolizinium compounds, MPB 102 and MPB103, in which Y of formula (Ia) is –SH. The two compounds include specific structural features, such as a chlorine atom at position 10, a thiol at position 6, and an n-butyl group at position 5. The particular combinations of structural features found in the two compounds claimed are neither taught nor suggested by the list of compounds found in claim 1 of Becq 2003.

In view of the amendments to the claims and the remarks above, Applicants request that the rejections for obviousness-type double patenting be withdrawn.

Support for Amendments to the Claims

Support for claim 23 is found in claim 2 as filed and in the specification from page 5, line 20, to page 6, line 10.

Support for claims 24-27 are found in the specification at page 2, lines 16-22, and at page 5, lines 15-19.

Support for claim 28 is found in the specification at page 6, lines 9-10; in claim 9 as filed; and in the specification at page 7, lines 25-35.

Support for claim 29 is found in the specification at page 6, lines 1-4.

Support for claim 30 is found in the specification at page 6, lines 1-4.

Support for claim 31 is found in the specification from page 6, line 16, to page 7,

line 35; from page 7, line 45, to page 9, line 35; and at page 10, lines 1-10.

Support for claim 32 is found in claim 10 as originally filed.

Support for claim 33 is found in claim 11 as originally filed.

Support for claim 34 is found in claim 17 as originally filed.

Support for claim 35 is found in claim 20 as originally filed.

Support for claims 36 and 37 is found in claims 21 and 22 as originally filed.

No new subject matter has been added with these amendments.

CONCLUSION

Applicants submit that this case is now in condition for allowance, and such action is respectfully requested.

Enclosed is a Petition to extend the period for replying to the Office action for 3 months, to and including July 8, 2008, and a check in payment of the required extension fee.

To expedite prosecution Applicants request a telephonic interview with the Examiner to discuss any remaining rejections. The Examiner is invited to call the undersigned at 617-428-0200.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: July 8, 2008

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HISTORICAL NOTE

Contractility of lungs and air-tubes: experiments performed in 1840 by Charles J.B. Williams

J. Lötvall

Contractility of lungs and air-tubes: experiments performed in 1840 by Charles J.B. Williams. J. Lötvall. ©ERS Journals Ltd 1994.

ABSTRACT: In the 18th century, some medical practitioners considered the main pathological feature of asthma to be the production of mucus. Later, during the 19th century, airway smooth muscle contraction was recognized to be a possible cause of airflow obstruction. However, not until 1840 was the contractility of airway smooth muscle clearly established by Charles J.B. Williams, a famous London physician.

In a number of innovative experiments in dogs, rabbits, livestock and even donkeys, he showed: 1) that airways contract in response to electrical stimulation; 2) that the observed contractions are almost totally abolished by belladonna and stramonium (anticholinergics); 3) that the responses faded over time; and 4) that morphine inhibited the observed responses. Application of irritant fluids into the tracheal lumen produced similar responses.

These interesting observations made by Williams will be reviewed, and related to current theories concerning modulation of airway smooth muscle responsiveness. *Eur Respir J., 1994, 7, 592–595.*

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Since the time of SALTER [1], airway smooth muscle contraction has been considered to be one of the most important contributors to the obstructive symptoms of asthma, whereas mucus production was considered to be an important cause of asthma by some earlier medical practitioners [2]. During the first half of the 19th century, however, it was known that the bronchial walls contain muscular elements, but the capacity of these muscles to contract was not well established [3, 4]. This question was, therefore, experimentally approached by Charles J.B. Williams in the summer of 1840, for which purpose he had been engaged by the British Association for the Advancement of Science [3, 4]. The results were published both in the reports of the Association [3], and in the fourth edition of a book on diseases of the chest by WILLIAMS [4]. As it turned out, these exciting original experiments, performed at University College, London, established some important regulatory mechanisms in the airways that are still being investigated in laboratories all over the world.

Charles J.B. Williams

Charles J.B. Williams (1805–1889) was a prominent 19th century London physician, with a great interest in the pathophysiology of asthma. Son of a clergyman, Williams studied medicine in Edinburgh, starting in 1820, and received his M.D. thesis in 1824. After a brief period in London in 1824–1825, Williams pursued his clinical career by spending one year in Paris, studying mainly with Laënnec [5, 6]. Williams was considered to be one of the most eminent lung physicians in mid-19th century London. As early as 1835, Williams was elected Fellow of the Royal Society, after being introduced by Faraday. However, the election of Williams was not without opposition, and, as it turned out, his contribution to the Society has been very small. One reason, mentioned by Williams in his memoirs, was that he was disappointed when the first paper that he submitted to the Society was refused, and was therefore deterred from offering any other papers in the future. Later in life, Williams strongly criticized the procedure of the election of Fellows, an opinion that may have further decreased Williams' contributions to the Society. Instead, he preferred the younger British Association for the Advancement of Science.

In 1839, Williams was elected Professor of Medicine at University College, London, and in 1840 he became Fellow of the Royal College of Physicians. Williams made a large contribution to the early development of pulmonary medicine, and took an active part in founding the Brompton Hospital in Chelsea, together with Philip Rose (later Sir) [7]. Williams became the first president of both the Pathological Society (1846) and the New Sydenham Society (1858).

Williams contributed to the education of medicine with two major textbooks. "A Rational Exposition of the

Physical Signs of Diseases of the Chest", was published as early as 1830, only 10 yrs after he started his medical studies in Edinburgh. Further volumes were published in 1833, 1835, and 1840, and the title was changed with the third edition to the more ambitious "The Pathology and Diagnosis of Diseases of the Chest; a Rational Exposition of their Physical Signs". In 1843, the first of three editions of "Principles of Medicine" was published, a popular and very successful standard textbook. Williams also accumulated a large amount of material on diseases of the chest, and started to work on a textbook on this subject, together with Richard Quain, but unfortunately, this comprehensive work, never appeared in published form.

When reading Williams memoirs and articles about him, one receives the impression that he was an extremely knowledgeable and thorough physician, and very highly regarded by his colleagues and patients. However, he also seems to have been quite provocative and radical, as evidenced from the various controversies in which he was engaged from time to time. His criticism of the Royal Society, has been mentioned previously, but he also argued strongly for reforms of the Royal College of Physicians, which aroused powerful emotions among many of his contemporary colleagues. The antagonism against him may be illustrated by the fact that the pages containing his obituary (Lancet 1889 issue) have been removed from the edition in the Royal College Library, perhaps by someone opposed to his ideas. He also had a famous controversy with Hope, with regard to the originality of certain experiments on the sounds of the heart, and with other colleagues on the diagnosis of the illness of the famous surgeon, Liston. All these controversies attracted great attention at the time, and may to some degree illustrate Williams' personality.

Not only was Williams an extraordinary physician and prominent person in 19th century England, but he was also one of the greatest early researchers in the field of respiratory medicine. Possibly, one of his most important contributions to basic respiratory science at the time are his observations concerning the contractility and modulation of tracheobronchial smooth muscle. In fact, some of his observations have been rediscovered in recent years, and their important role in airway physiology is now becoming well-established.

Methodology

In his report to the British Association for the Advancement of Science, Williams described the methods he used to study the contractility of airway musculature [3, 4]. Most experiments were performed on lungs removed from dogs, killed by pithing, a blow to the head, bleeding or injection of various substances such as morphine, stramonium or belladonna (active ingredient of which is atropine). The lungs were in most instances taken out, together with a portion of the trachea, which was connected to a manometer filled with coloured liquid. In a few experiments, the lungs were left in the body of the animal while stimulated. The trachea and/or lungs were then exposed to various stimuli, including galvanic current (thirty three inch plates) and irritant liquids. The response was measured by observing the manometer and measuring the rise of the liquid in inches and tenths. Irritant liquids were delivered to the airway lumen, through the manometer, or applied directly to the bronchial lumen when the lungs had been opened. The irritants used were diluted ammonia and strong salt solutions.

In Williams' publications, he presents the source of all materials used, as we do today. All extracts used were obtained from Squire, Chemist to H.M. the Queen. However, references to previous scientific literature are not given with the same care.

Contraction of tracheobronchial muscle

On applying an electric current over the trachea and lungs, Williams found that a prompt increase in the airway luminal pressure was induced, observed as a rise of the liquid in the manometer connected to the trachea. "On passing a galvanic current, from a trough of thirty three-inch plates, from the margin of the lungs to the brass tube in the trachea, the fluid rose quickly, but gradually ...". This experiment was repeated in eight dogs of various sizes, with similar results, and the rise of the fluid column caused by galvanizing the whole lung amounted to 1.5 to 2.5 inches.

In some instances, parts of bronchi or trachea were removed from the lungs, opened longitudinally, and exposed to the galvanic instruments. When this was done, a contraction of the membraneous part of the airway wall was observed. Furthermore, the diameters of exposed bronchi were measured during galvanic stimulation, which produced clear narrowing, sometimes to half, and in some instances to less than half their former diameters.

With these basic experiments, the contractility of the tracheobronchial tree was firmly established. As has been proved since, the contractions induced by electrical stimulation over airway smooth muscle are usually induced by activation of nerves, as tetrodotoxin (TTX), a specific nerve toxin, inhibits nerve-induced contractile responses [8]. However, Williams found it difficult to induce contraction of the airways by direct stimulation of the vagi. In one experiment, leaving the lung in the body, no effect was seen when one vagus was pinched or, subsequently, when a galvanic current was applied over the other vagus. However, a small rise of the liquid in the manometer was found "when the nerve was separated and the galvanism was passed through it to the base of one lung". This lack of responsiveness to vagal nerve stimulation may be explained by the type of stimulation used, although it is not clear exactly how Williams was stimulating the tissues electrically. It seems that a direct current galvanometer was used, although the stimulator was not described in detail in the publications. In modern studies of airway nerves, alternate current is used for repeated stimulation, whereas direct current may act directly on smooth muscle cells and may also damage tissues, such as the vagal nerves in the experiment just

mentioned. It is possible that some of Williams' observations were due to direct effects on non-neural tissues, although there is indirect evidence of an activation of cholinergic nerves in these historical experiments.

Cholinergic mechanisms

In experiments evaluating the effects of belladonna and stramonium, both potent antimuscarinic compounds, an inhibitory effect of the muscle shortening induced by electrical stimulation was observed. Dogs or rabbits were killed with extracts of belladonna or stramonium injected into the jugular vein or neck tissue. When the lungs had been removed "galvanism produced no effect for several minutes, and then a scarcely perceptible rise". Thus, a major proportion of the observed contractile responses was due to the release of acetylcholine from airway cholinergic nerves. The nature of the remaining small responses observed by Williams are not clear, and could be due to tissue damage, or perhaps, more excitingly, to non-cholinergic mechanisms, for example the release of tachykinins [9].

To Williams, the potent inhibitory effects on "air-tube contractility" of stramonium and belladonna explained their efficacy in asthma. Stramonium was introduced from India in the first years of the 19th century [1, 10], and was considered by contemporary authorities on lung diseases to be a superior remedy for the treatment of spasmodic asthma [1, 3–5]. Williams believed that the superior efficacy of stramonium and belladonna in spasmodic asthma was due to a general inhibitory effect of these drugs on the bronchial muscles. We have since recognized that the inhibitory effects of these compounds are localized to muscarinic receptors; receptors on airway smooth muscle and glands that are activated upon release of acetylcholine from cholinergic vagal fibres.

Fading of responses

When the contractility of the bronchial muscle had been established, one of the first observations that Williams made was that prolonged electrical stimulation led to fading of the response. He wrote: "the fluid rose quickly, ... but fell slowly when the contact was continued for some seconds ... The rise was repeatedly produced, but to a diminishing extent, and after two or three minutes the effect seemed to be exhausted". A fading similar to the type observed by Williams has been extensively studied in recent years, and is currently believed to be due to inhibitory factors released from airway epithelium. Thus, a fading of nerve-induced contractions of tracheobronchial muscle, similar to that observed by Williams, is seen only in the presence of airway epithelium [11]. The inhibitory substances produced by the epithelial cells are now believed to be both prostaglandin E_2 (PGE_2) and possibly non-prostanoid factors [11–13]. Epithelial damage may eliminate the production of inhibitory factors from the epithelium, which may be one important underlying mechanism of nonspecific bronchial hyperresponsiveness in asthma [13]. However, it should be emphasized that the fading of the responses in Williams' experiments could be due to tissue damage and the release of toxic substances upon the crude electric stimulation.

Inhibition by morphine

It has recently been shown that cholinergic nerve-induced contraction of guinea-pig trachea is inhibited by opioids, a mechanism that has been suggested to be localized to the nerves prejunctionally [14]. However, similar observations were made by Williams in his early experiments. He found that when a dog was injected with a high dose of an extract of opium before the lungs were removed, the galvanic current "only raised the dynameter slightly, not more than a tenth ... much less than in other cases". Opioids were, at that time, sometimes used in the treatment of asthma, and any beneficial effect may in some cases be explained by the inhibition of airway nerves, an effect that was originally discovered by Williams in 1840.

Exposure to irritants

The capacity of irritant gases to induce obstructive symptoms in patients with asthma were well known to Williams. To study this observation in his experimental system, Williams poured the irritating fluid into the lumen of the trachea through the manometer, and observed small responses, which he considered were produced by the irritating liquid. However, "viscid froth" was also collected in the bronchi by these irritants, which Williams believed had impeded the observed responses in the manometer.

To study bronchial responsiveness today, we often give inhaled irritants, such as ozone, SO_2, sodium metabisulphite, or hypertonic solutions, to asthmatic patients [15]. The observation made by Williams that saturated salt solutions contract airway smooth muscle, may have been the first finding of bronchoconstriction to a hypertonic solution.

Conclusions

Charles Williams effectively summarized his experiments: "I trust that many of the results of the preceding experiments are sufficiently evident without further comment. Almost all of them prove that the air-tubes are endowed with irritable contractility, excitable by electric, chemical, and mechanical stimuli, and they possess also tonic contractility. The contractility is manifest in all portions of the air-tubes. In the trachea and larger bronchi it is antagonised by the elasticity of the cartilaginous rings. It does not appear to exist in the vesicular terminations of the air-tubes ... The irritability of the bronchial muscles is soon exhausted by the action of a stimulus, and may in some degree be restored by rest, even when the lung is removed from the body

for an hour or more. But when the stimulation is long continued, as by intense irritation of the mucous membrane during life, the irritability is not restored by rest, and the tonic contractility is also impaired ... Several vegetable poisons impair or destroy this contractility. Extracts of stramonium and belladonna produced this effect most completely ... morphia also impair this property considerably ...".

In his memoirs, Williams states: "In animals ... poisoned by belladonna or stramonium, this contractility of the tubes was almost destroyed, giving no signs of movement under galvanism. In animals poisoned by opium and by strychnia, it was impaired, but not destroyed; confirming the fact, well known to the experienced practitioner, that these are inferior to belladonna and stramonium as remedies for the spasm of asthma".

These experiments, performed by Williams, are obviously important hallmarks of science, clearly showing that the muscle of the airway wall can contract upon electrical stimulation (most likely nerve-induced effects). Although not aware of the importance of nerves in the observed responses, Williams found that the airway contractility was almost abolished by anticholinergics (thus mediated *via* the activation of cholinergic nerves; [16]). He also discovered the fading over time of responses induced by galvanic current, effects that have recently been shown to be due to inhibitory factors released from the airway epithelium [11–13].

Furthermore, application into the airways of irritants, such as saturated salt solutions, were found to produce frothy viscid mucus, as well as contraction of bronchial muscle. Lastly, Williams established an inhibitory effect of opioids in the airways, which has recently been localized to airway nerves [14].

Charles J.B. Williams, being well before his time, deserves to be remembered as one of the most important contributors to our current knowledge of airway pathophysiology.

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Are asthmatics salt-sensitive? A preliminary controlled study

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Are Asthmatics Salt-Sensitive?*

A Preliminary Controlled Study

Tullio C. Medici, M.D.; Adrienne Zumstein Schmid, M.D.; Martin Häcki, M.D.; and Wilhelm Vetter, M.D.

Objective: Epidemiologic evidence suggests that high levels of salt consumption are associated with "spastic" disorders of smooth muscles, *ie*, essential hypertension and bronchial asthma. Experimentally, it has been shown that high intake of salt leads to increased bronchial hyperreactivity in asthmatics, *ie*, enhanced contractility of bronchial muscle to spasmogenic stimuli. On the basis of these observations, the following questions were asked: (1) Does salt loading worsen the clinical and functional findings in asthmatics? (2) Is it the sodium or the chloride in salt that is important?

Methods: To answer these questions, the effect of salt restriction (=5 to 6 g NaCl/d=86 to 103 mmol Na), salt loading (+6.1±2.8 g NaCl/d=+105±48 mmol Na), and loading with sodium citrate in nearly equimolar concentrations (+140±40 ml Shohl's solution, =+120±30 mmol Na) was investigated in 14 asthmatics in a controlled crossover study. The total sodium load during the high salt diet was 191 to 209 mmol of sodium per day and during the sodium-citrate phase, 206 to 223 mmol of sodium per day.

Results: Statistical analysis showed that salt loading worsened symptoms ($p=0.06$) and increased the use of inhaled steroids ($p<0.05$). The effect on lung function was less equivocal: salt loading worsened the forced expiratory volume in 1 s ($p<0.01$) and the peak expiratory flow rate ($p<0.05$). This effect was presumably mediated by sodium, not chloride, as is demonstrated by loading with sodium citrate.

Conclusion: Patients with bronchial asthma seem to be salt-sensitive, the responsible ion being presumably sodium. A low-salt diet appears to have a favorable effect in patients with asthma and to reduce the need for antiasthma drugs.

(Chest 1993; 104:1138-43)

PEFR = peak expiratory flow rate

As in the case of essential hypertension, there is a marked geographic variation in asthma prevalence and mortality.[1-3] The regions where bronchial asthma prevalence and mortality are higher are countries of Western-style culture with advanced technology, which differ from poorer and technologically less developed regions in several respects. One of these is eating habits, in particular, a higher salt intake.[3,4] In fact, on the basis of the salt consumption in 39,000 English households, Burney[5] showed the more salt that was bought and thus used per week, the higher the mortality in asthmatics.

Experimentally, salt intake appears to influence bronchial hyperreactivity. When asthmatics were loaded with sodium, the histamine provocation dose decreased and the hyperreactivity increased. When they were receiving a low-salt diet, the opposite occurred.[6,7]

On the basis of these epidemiologic and experimental observations, we asked ourselves the following questions: (1) Does quantitative salt loading worsen the clinical and functional findings in asthmatics and conversely, does salt restriction improve them? (2) Is it the sodium or the chloride in the salt that is important for the effect? This question arises because the chloride in salt is necessary to raise blood pressure in salt-sensitive hypertensives.[8] In order to answer these questions, a controlled crossover study was initiated to investigate the effect of salt loading and salt restriction in asthmatics. In a second phase, sodium citrate in equimolar concentrations was given instead of sodium chloride.

Methods

Patients

The inclusion criteria required eligible patients to be at least 16 years of age and to fulfill the American Thoracic Society criteria for the diagnosis of asthma.[9] Exclusion criteria were as follows: instability of asthma, therapy with oral steroids, cromoglycan or diuretics, other concomitant disease (cardiac insufficiency or arrhythmia, liver or kidney disease, diabetes mellitus), and pregnancy. Moreover, we excluded asthmatics who were currently smokers.

Eighteen patients were assessed and agreed to participate in the trial. Of these, four (two women, two men) were excluded during the run-in phase because of poor compliance. The final study group included 14 nonsmoking men (n=9) and women (n=5) (aged 20 to 65 years), with stable atopic or mixed-type bronchial asthma, mild reversible airways obstruction, and confirmed atopy (positive skin test, positive radioallergosorbent test). Informed consent was obtained from all patients. The study was approved by the ethical commission of the hospital.

Study Design

During a 2-week run-in period (Fig 1), a dietitian started the asthmatics on a low-salt diet (5 to 6 g/d=86 to 103 mmol of sodium), which was maintained throughout the study. The patients kept a diary in which they made a daily record of asthma attacks, peak flow measurements, and medication taken. The inhaled antiasthma drugs used were salbutamol (100 μg/puff) or terbutaline (200 μg/

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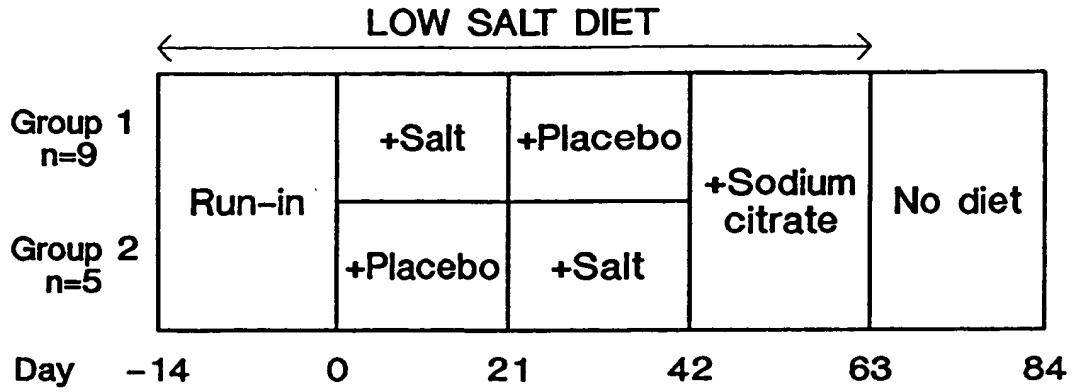

FIGURE 1. Design of study Low-salt diet = 5 to 6 g sodium chloride per day = 86 to 103 mmol sodium. Salt = +9 g sodium chloride (3×3 capsules) per day = 154 mmol sodium. Placebo = + lactose (3×3 capsules) per day. Sodium citrate = + 180 ml Shohl's solution (3×60 ml) per day = + 154 sodium.

puff) on demand and beclomethasone (250 μg/puff) or budesonide (200 μg/puff) on a regular basis. In case of improvement or deterioration of asthmatic symptoms or peak flow values, patients were told to increase or decrease doses of their inhaled β-sympathicomimetics and steroids. Theophylline was used when necessary. Peak flow measurement using a peak flow minimeter (Wright) was carried out morning, noon, and evening, before bronchodilator use. The best of three peak flow measurements was recorded. The patients were randomized into two groups after the run-in period. During the first 3-week treatment period, they received daily nine capsules containing either 1 g of sodium chloride or placebo (lactose). The patients were instructed to swallow the entire capsule. The addition of 9 g of salt per day resulted in a total amount of 14 to 15 g of salt, *ie*, 240 to 257 mmol of sodium. At the end of the 3 weeks, the cross-over was made without a wash-out phase, and a second 3-week treatment period followed. Finally, instead of either sodium chloride or placebo, the patients were given sodium citrate in an equimolar concentration (+180 ml Shohl's solution per day = 154 mmol Na) for 3 weeks. Adding 180 ml of sodium citrate per day to the low-salt diet resulted in a total amount of 240 to 257 mmol of sodium. When all the treatment periods had been completed, the patients were followed up for a further 3 weeks while receiving a normal diet.

Clinical check-up (examination, weight check), lung function tests, and electrolyte determination (sodium, potassium, chloride, including creatinine) in serum and 24-h urine were carried out 2 weeks before (day −14) and at the beginning (day 0) of the study, and then at intervals of 10 to 11 days (days 10/11, 21, 31/32, 42, 52/53, 63, 73/74, 84). Methacholine tests and determination of hematologic values (blood cell count, including eosinophils, serum immunoglobulin E [data not shown]) were performed on days −14 and 0, and then every 3 weeks (days 21, 42, 63, 84). The methacholine test was carried out under standardized conditions.[10] Spirometric and flow measurements were made in the morning at the same interval before and after inhalation of 300 μg of salbutamol. The laboratory personnel performing the pulmonary function tests and blood tests were not informed about the salt regimens of the patients.

As criteria of efficacy of salt loading and salt restriction, the number of asthmatic attacks, self-measured peak flow rate, use of antiasthma drugs, spirometric values, and the dose of methacholine provoking a 20 percent decrease of FEV_1 were chosen.

Statistical Analysis

Mean values and standard deviations were calculated. The results of the two-phase cross-over were analyzed according to the model of Grizzle[11] and Koch,[12] comparing the intraindividual treatment differences (phase 2 minus phase 1) between the cross-over groups (Table 1: effect of sodium chloride). The third phase with intake of sodium citrate was evaluated by paired difference comparisons regarding the previous placebo phase (sodium effect) and sodium chloride phase (chloride effect), respectively (right part of table 1). The significance of the differences was calculated by means of nonparametric one-sided tests (Wilcoxon-Mann-Whitney test and Wilcoxon paired test); the significance threshold for the tests of efficacy was defined as $\alpha = 0.05$ ($p = 0.05$). The application of the

Table 1—*Effects of Different Sodium Regimens on Symptoms, Use of Antiasthma Drugs, and Pulmonary Function in 14 Asthmatic Patients (Means ± SD)**

	Run-in	Two-Period Crossover		Sodium Phase	
	No Diet (Day-14)	Low-Sodium Diet "Baseline" (Day 0)	Low-Sodium Diet + Placebo (Day 21/42)	Low-Sodium Diet + Sodium Chloride (Day 21/42)	Low-Sodium Diet + Sodium Citrate (Day 63)	Follow-up No Diet (Day 84)
Asthma attacks, No./last 10 d	ND	2.3 ± 3.97	2.3 ± 3.36	4.0 ± 4.15	6.4 ± 17.0	0.9 ± 1.83
PEFR, L/min,† mean over 5 d	ND	380 ± 74.2	381 ± 65.6	374 ± 68.6	373 ± 58.7	376 ± 69.0
β-mimetics, sprays/d	ND	4.3 ± 1.52	4.1 ± 1.65	5.1 ± 2.78	4.5 ± 1.85	4.2 ± 1.89
Corticosteroids, sprays/d	ND	2.7 ± 1.88	2.3 ± 1.91	2.9 ± 1.90	2.4 ± 1.92	2.6 ± 1.79
FEV_1, L	2.44 ± 0.84	2.41 ± 0.76	2.57 ± 0.86	2.30 ± 0.79	2.37 ± 0.81	2.33 ± 0.83
FEV_1/VC, %	65 ± 13	65 ± 12	67 ± 13	64 ± 13	64 ± 11	65 ± 13
PEFR, L/s	6.50 ± 1.93	6.44 ± 1.81	6.64 ± 2.02	6.27 ± 1.91	6.06 ± 2.08	6.23 ± 2.04
PD20, log μg	4.7 ± 1.23	4.6 ± 0.96	4.4 ± 0.87	4.7 ± 0.99	4.2 ± 0.79	4.3 ± 0.90

*ND = not done (delivery of patient's diary only); FEV_1 = forced expiratory volume in 1 s; VC = vital capacity; PEFR = peak expiratory flow rate; PD20 = μ microgram methacholine provoking a 20 percent decrease of FEV_1 (at baseline n≤10; later on n = 13).
†Measured by patient.

Table 2—*24-h Urinary Electrolyte Excretion, Serum Electrolyte Content, Weight, and Blood Pressure in 14 Asthmatic Patients Receiving Different Sodium Regimens (Means ± SD)*

	Run-in		Two-Period Crossover		Sodium Phase	
	No Diet (Day-14)	Low-Sodium Diet "Baseline" (Day 0)	Low-Sodium Diet + Placebo (Day 21/42)	Low-Sodium Diet + Sodium Chloride (Day 21/42)	Low-Sodium Diet + Sodium Citrate (Day 63)	Follow-up No Diet (Day 84)
Urine						
24-h sodium excretion, mmol/L	119 ± 54	107 ± 53	79 ± 38	137 ± 45	134 ± 62	110 ± 54
24-h chloride excretion, mmol/L	112 ± 54	110 ± 50	84 ± 38	131 ± 45	89 ± 79	110 ± 58
Serum						
Sodium, mmol/L	144 ± 8.31	140 ± 5.71	141 ± 5.80	143 ± 3.87	142 ± 5.38	142 ± 2.82
Chloride, mmol/L	101 ± 7.22	103 ± 7.24	105 ± 6.84	105 ± 4.83	103 ± 5.54	103 ± 6.18
Weight, kg	68.3 ± 12.4	67.2 ± 11.8	68.6 ± 12.7	69.2 ± 13.1	67.4 ± 12.9	67.9 ± 13.1
Blood pressure, mm Hg						
Systolic	133.7 ± 20.3	131.2 ± 22.7	131.6 ± 15.8	135.4 ± 23.0	132.3 ± 13.7	130.2 ± 12.1
Diastolic	82.6 ± 10.9	80.4 ± 12.0	80.9 ± 10.2	80.7 ± 15.8	80.7 ± 9.39	83.4 ± 8.92

statistical model was verified by former testing for carry-over effects ($\alpha = 0.10$).

Results

The descriptive statistical results are presented in a simplified manner that allows global insight into the effects of sodium chloride and sodium citrate loading for all patients (Tables 1 and 2). Due to side effects (heartburn) in the first few days of salt loading, less than the intended additional 9 g of salt per day were used. However, the variation in salt, placebo, and Shohl's solution intake was confined within narrow limits: on average, 6.1 ± 2.8 salt capsules (= +105 ± 48 mmol sodium), 6.3 ± 4.2 placebo capsules, and 140 ± 40 ml sodium citrate (= +120 ± 30 mmol sodium) were taken daily. The total sodium load during the high-salt diet was then 191 to 208 mmol of sodium per day and during the sodium-citrate phase, 206 to 223 mmol of sodium per day, approximately twice the sodium load of the low-salt diet (86 to 103 mmol of sodium).

The results regarding the efficacy criteria are com-

Table 3—*Statistical Analysis of the Effects of Different Sodium Regimens on Symptoms, Use of Antiasthma Drugs, and Pulmonary Function in 14 Asthmatic Patients**

			Two-Period Crossover Effect of Sodium Chloride			Sodium Phase			
				Mann-Whitney		Effect of Sodium		Effect of Chloride	
	Group	N	Mean ± SD	r	p	Mean ± SD	Wilcoxon p	Mean ± SD	Wilcoxon p
Asthma attacks, No./last 10 d	NaCl→Placebo	9	−1.8 ± 3.90	6.2	p = 0.06	+4.1 ± 16.0 (n = 14)	NS	−2.4 ± 15.1 (n = 14)	NS
	Placebo→NaCl	5	+1.6 ± 4.72	9.9					
PEFR, L/min,† (day before visit)	NaCl→Placebo	9	−8.9 ± 31.7	9.2	≤0.05	−28.0 ± 40.1 (n = 14)	≤0.05	+16.5 ± 49.0 (n = 14)	NS
	Placebo→NaCl	5	−48.0 ± 42.0	4.4					
β-mimetics, sprays/d	NaCl→Placebo	9	−0.38 ± 1.01	6.4	NS	+0.40 ± 1.34 (n = 14)	NS	+0.59 ± 2.53 (n = 14)	NS
	Placebo→NaCl	5	+2.07 ± 4.67	9.4					
Corticosteroids, sprays/d	NaCl→Placebo	9	−0.54 ± 0.67	6.1	≤0.05	+0.10 ± 1.74 (n = 14)	NS	+0.53 ± 1.63 (n = 14)	NS
	Placebo→NaCl	5	+0.80 ± 1.35	10.0					
FEV_1, L	NaCl→Placebo	9	+0.13 ± 0.498	9.8	≤0.01	−0.20 ± 0.379 (n = 14)	≤0.05	−0.06 ± 0.312 (n = 14)	NS
	Placebo→NaCl	5	−0.51 ± 0.279	3.4					
FEV_1/VC, %	NaCl→Placebo	9	+1.73 ± 4.52	ND		−2.65 ± 5.87 (n = 14)	≤0.05	−0.61 ± 5.88 (n = 14)	NS
	Placebo→NaCl	5	−6.00 ± 8.96						
PEFR, L/s	NaCl→Placebo	9	−0.12 ± 0.98	9.0	≤0.05	−0.58 ± 0.906 (n = 14)	≤0.05	+0.21 ± 0.924 (n = 14)	NS
	Placebo→NaCl	5	−1.26 ± 1.07	4.8					
PD20, log μg	NaCl→Placebo	9	−0.50 ± 0.716	6.1	NS	−0.19 ± 0.659 (n = 13)	NS	+0.50 ± 0.671 (n = 13)	NS
	Placebo→NaCl	5	−0.01 ± 0.487	8.4					

*FEV_1 = forced expiratory volume in 1 s; VC = vital capacity; PEFR = peak expiratory flow rate; PD20 = microgram methacholine provoking a 20 percent decrease of FEV_1; Mann-Whitney = comparison of crossover groups (r = mean rank); Wilcoxon = intraindividual comparison of day 63 with placebo treatment at day 21/42 (sodium effect) or with sodium chloride treatment at day 21/42 (chloride effect), respectively; NS = not significant ($p \geq 0.10$); ND = not done because of eventual carry-over effect.

†Measured by patient.

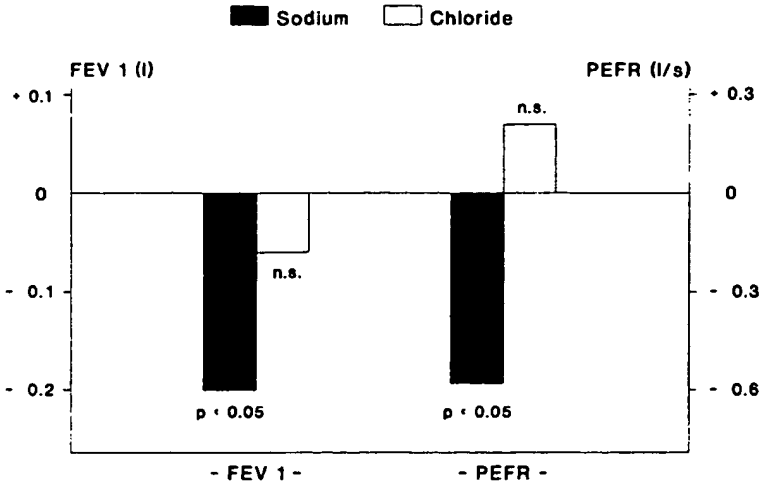

FIGURE 2. Effect of sodium and chloride on FEV_1 and PEFR comparing the sodium phase with intake of placebo and sodium chloride, respectively (mean changes; Wilcoxon-test/n = 14).

piled in Tables 1 and 3. Although the changes observed were small, some reached statistical significance despite the small number of patients. The statistical analysis (Table 3) showed an influence of the salt intake on both number of asthma attacks and use of inhaled β-sympaticomimetics and steroids: salt loading increased the frequency of attacks and the use of inhaled antiasthma drugs. However, only the increase of inhaled steroids was statistically significant, while the increase in the number of asthma attacks narrowly missed significance ($p = 0.06$).

The effect of salt on lung function was clearer. The peak expiratory flow rate (PEFR) measured by the patient decreased with salt intake. This effect was also observed under sodium citrate loading, indicating a sodium-mediated effect. Interestingly, the change of the peak flow (mean of the best values obtained in the morning, noon, and evening) was significant only on day 1 and day 5 before examination, but not on day 2 to 4 (mean change of last 5 days before visit not significant). In correspondence with the effect of salt on the PEFR measured by the patient, both this lung function value and the FEV_1 measured in the laboratory decreased significantly with the salt and sodium citrate loading, being probably a sodium-mediated effect ($p<0.05$, Table 3). Statistical comparison with the NaCl phase did not show a chloride-mediated effect (Fig 2). No such effects could be established as regards the methacholine dose required to induce a 20 percent drop in FEV_1 (PD 20), *ie*, as regards bronchial hyperreactivity.

As expected, 24-h sodium and chloride excretion in the urine decreased during low-sodium diet and increased during salt loading (Table 2). The addition of sodium citrate increased sodium but not chloride excretion. The sodium and chloride content in serum remained unchanged. This was also true for blood pressure. Weight increased slightly during salt loading, the change being statistically insignificant.

DISCUSSION

Epidemiologic and experimental evidence suggests that high levels of salt consumption are associated with "spastic" disorders of smooth muscles, *ie*, essential hypertension and bronchial asthma. This observation stems from migration studies, such as those on the inhabitants of Tokelau, as well as in studies from industrialized countries with well-defined social conditions and environmental factors.[1-5] In the United States, blacks use more salt than whites,[13] and correspondingly more blacks suffer and die from asthma.[14] The prevalence of hypertension is also greater than in whites.[15]

Experimentally, it has been shown that high intake of salt leads to enhanced contractility of bronchial muscle to spasmogenic stimuli.[6,7] In hypertensives β-receptors of smooth muscles are down-regulated by salt-loading, leading to contraction.[16,17] Hence, salt sensitivity seems to be a common phenomenon of both disorders, at least in many patients.

The results of our study obtained in a small number of asthmatics support the hypothesis of salt sensitivity in asthmatics. When asthmatics were subjected to salt loading, asthma symptoms became worse, lung function deteriorated, and the use of antiasthma drugs increased. When salt intake was stopped, the opposite occurred. These effects were probably due to the sodium in the salt, as demonstrated by loading with sodium citrate. However, an effect of chloride could not be definitely excluded. In view of the small number of patients tested, a β-error is certainly present, which makes small effects indetectable. Moreover, the objection may be made that our results would be more unequivocal if asthmatic women were excluded, since women seem to tolerate salt loading better than men and children with asthma.[6] However, this has been disputed by Javaid et al.[7] Because of the small number of women asthmatics tested, the results were not statistically analyzed in regard to sex. Looking at the

individual data, women behaved similarly to men during loading with sodium.

In spite of these shortcomings, our results regarding salt loading and salt restriction are largely in agreement with those of Carey et al,[18] who used a similar design and similar dosages of salt in many more asthmatics. However, the role of the sodium ion as the possible culprit was not assessed by these authors.

The way in which increased salt intake, *ie*, sodium loading, exerts its effects in patients with bronchial asthma is unclear. However, there are data from *in vitro* and *in vivo* experiments that may explain the mechanisms of salt sensitivity. From the work of Souhrada and Souhrada[19,20] we know that after renewed antigen contact, sensitized bronchial muscle cells demonstrate an increased influx of Na^+ with consequent stimulation of the electrogenic Na^+-K^+ pump and hyperpolarization. The intracellular increase in Na^+ is associated with an increase in Ca^{++} and contraction of the muscle cell. The increase in intracellular sodium after increased sodium intake could occur directly, as despite the homeostatic mechanisms that minimize changes in extracellular sodium, small changes in plasma sodium are still apparent after several days of receiving a high-salt diet.[21] On the other hand and more likely, an increase in intracellular sodium could be produced by circulating inhibitors of Na^+/K^+ adenosine triphosphatase (Na^+/K^+-ATPase) in subjects taking a high-salt diet, the increase in the concentration of these inhibitors probably resulting from extracellular expansion.[22] In accordance with these observations Knox et al[23] showed that quabain, an inhibitor of Na^+/K^+-ATPase, caused contraction of bovine and human airways *in vitro*. *In vivo*, however, these authors were unable to produce a change in histamine responsiveness in asthmatics after inhaled quabain.[24]

Presumably, structures other than the smooth muscle cells may also be affected, since transcellular electrolyte and ion transport is a function of all living cells. Thus, the erythrocytes of asthmatics have been shown to have an increased Na^+ content.[25] All in all, these are indications of a probably generalized dysfunction of the cellular sodium regulation in bronchial asthma.

Another different explanation of the effect of salt on symptoms and pulmonary function in our patients could be water retention and overload as a consequence of salt loading. This may occur in patients with decreased urine output or subclinical left ventricular failure. However, none of our patients suffered from renal or cardiac disease. Moreover, weight did not change significantly during salt loading.

In conclusion, patients with bronchial asthma seem to be salt sensitive: salt loading was associated with deterioration of symptoms and lung function and increased use of antiasthma drugs. When salt intake was restricted, the opposite occurred. The effects were probably due to the sodium in the salt, not the chloride. A low-salt diet may have a favorable effect on asthma and may reduce the need for antiasthma drugs.

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